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## Etiology and treatment of physical allergy

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THE ETIOLOGY AND TREATMENT  
OF  
PHYSICAL ALLERGY

By

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## INTRODUCTION

Barber (1) states that allergy is beyond question one of the most important biological and medical problems that exist or ever has existed, for it represents the pathology of the reaction of man and the lower animals to their environment, to the air they breathe, the physical agents such as light, heat and cold to which they are exposed, the food they eat and the various parasitic organisms which may invade them.

It is well known that persons can become hyper-sensitive to a large variety of material substances and react whenever they come in contact with them. Some persons are so sensitive that they become ill on contact with minute traces of the agents to which they react. For example, those sensitive to buckwheat may be made ill by the trace of buckwheat in a drop of honey; infants sensitive to milk are frequently made ill, not by any of the usual constituents of milk, but by certain foods eaten by the woman or animal furnishing the milk. Patients who receive blood transfusions are occasionally made ill, or even shocked, by the introduction of one syringe of blood taken from a donor who has eaten some food to which the patient is sensitive.

While the diagnosis of allergic conditions has reached a fairly satisfactory basis, it is apparent to anyone who has given the matter serious thought, that these conditions are being treated symptomatically and that the fundamental abnormality responsible for the development of allergy remains untouched. That there is an inheritable factor seems to have been proven, but what it is that is inherited no one knows. What physical abnormality is

responsible for the functional disturbance? The answer to this would, in all probability, solve many of the problems, for many of those who have studied allergic conditions are coming to believe that the fundamental abnormality is the same in all allergic persons and the type of manifestation and the substance to which they react are matters largely of accident.

Man has probably been subject to allergy since his advent upon earth. Possibly the disease existed even before that time. Probably the oldest disease known to man is arthritis, this disease, writing it's record in bone, leaves permanent evidence which can be found later by archeologists. But the allergic diseases usually leave no permanent marks at all. Uncomplicated asthma and hay fever, once the attack is over, leave no great evidence of damage. Hives subside, with no trace remaining. In early historic times skin diseases were looked upon as all being very much alike (20), such general terms as leprosy, scrofula and eczema being used to include most of them. Only in the past decade has medicine been able to differentiate many of these skin diseases upon a scientific basis. Asthma and hay fever have been known for some time. W. W. Duke (1926) states that at one time, he thought that cases of physical allergy were examples of the rarest illness. One year's search for cases of a similar nature, however, convinced him that patients who react to and are made ill by the action of a physical agent should be an every day finding in a busy physicians office.

Hallum (18) states that many men in the middle of the last century fully recognized the diversity of the causes of the urti-

carial reaction, and that in every text book, ancient and modern, there is a long list of both external and internal causes, and that almost every close observer can add to the list. He states that Crocker, in 1893, quoted a case of urticaria in which a ring at the front door would determine an attack. The original description of urticaria in the literature, according to Pusey (23), was by Bannister, who accurately described it's symptomatic character. (Chicago Medical Review, June 20, 1880) The original description of urticaria is usually credited to Quincke (Monatshefte f. prakt. Derm. u. Syph., 1882).

In 1904, Dr. Osler (24) brought together twentynine cases which he entitled "On the Visceral Manifestations of the Erythema Group of Skin Diseases." In this group was a remarkable form of urticaria which came on after the exposure to cold. So long as the face of the patient was at a temperature of above 60 degrees F, the patient was all right; exposure at 40 degrees was felt at once by an outbreak of urticaria. In 1905, Ward of Albany (28) reported a case of erythema and urticaria caused only by exposure to the sun's rays.

From a study of the literature, as above, we find that at about the beginning of the present century there was a gradual increase in interest or in recognizance of the physical allergies. From this time on up to the present day there has been a more or less gradual increase in this interest. The general knowledge of this group of diseases, now recognized as not uncommon, has been much added to by Duke of Kansas City, from his extensive clinical studies, and by various investigators from over the United States

and Europe, whose names and work will be mentioned in the body of this study.

In this paper, I shall deal not with illnesses caused by sensitiveness to material substances, but with illnesses of a similar nature, caused by sensitiveness to the action of physical agents such as light, heat, cold and mechanical irritation. The discussion will be confined for the most part to those factors in the etiology and treatment in so far as I am able to present them from a survey of the literature upon the subject.

## CLASSIFICATION AND DESCRIPTION

In order to impress the reader with the large variety of causes of the symptom urticaria, before limiting the discussion to just one factor, I will present a brief classification of the various urticarias, as given by Hopkins and Kesten (21):

1. Urticaria caused by physical agents.
2. Urticaria from internal causes.
3. Serum sickness. (Reaction to horse serum)
4. Urticaria caused by food. (Specific foods)
5. Urticaria caused by drugs.
6. Urticaria from bacteria and fungi.
7. Urticaria due to animal parasites and to biting insects.
8. Urticaria from metabolic causes.
9. Endocrine urticaria. (With menstrual periods)
10. Psychogenic urticaria.

At the end of this paper are presented three case summaries which represent a few of the various types of reactions due to physical allergy. Duke (11) has classified the types of cutaneous reactions caused specially by the action of physical agents as follows:

### I. Contact Reactions.

#### A. Immediate reactions.

1. Urticaria solaris (caused by light).
2. Urticaria dermatographica (caused by friction).
3. Urticaria hiemalis (caused by heat).



B. Delayed Reactions.

1. Dermatitis.

C. Solitary Reactions.

1. Wheals and papules.

II. Reflex-like Reactions.

A. Immediate reactions.

1. Urticaria Calorica (caused by heat).
2. Urticaria frigore (caused by cold).

B. Delayed reactions.

1. Dermatitis.

C. Solitary reactions.

1. Wheals and papules.

In Duke's definition of physical allergy, he states that it is a "name" suggested for altered reaction caused specifically by the physical agents, those above mentioned, and in the case of heat sensitiveness, "indirectly" by the effect of mental or physical exertion. The reactions produced are of two varieties, (a) contact reactions in which the reaction is confined to the point of contact between a surface and the irritating agent, and (b) reflex reactions which occur not only at the site of contact but in distant structures as well. General symptoms may always follow the contact if the surface exposed is large enough.

The contact reactions represent a distinct type of reaction (12), the characteristics of which may be described as follows:

1. The patients almost invariably give a family history of hay fever, asthma, hives, or other manifestations of allergy (90 per cent of cases studied by Duke), but <sup>not</sup> caused

in other members of the family by sensitiveness to physical agents.

2. The reaction is characterized by erythema, itching, and edema (the wheal) which can be brought out specifically and solely by the action of a physical agent to which the patient is hyper-sensitive. In mild cases long exposures may cause dermatitis.
3. The hive reaction does not spread with pseudopod formation far beyond the area directly exposed to the irritating agent. The erythematous reaction, however, spreads indefinitely over irregular areas.
4. Sensitiveness appears usually prior to middle life.
5. The condition does not vary greatly in intensity from time to time.
6. The condition once established is permanent.
7. The skin can be exhausted locally by reaction so that further exposure of a given area of skin to the irritating agent on the same day has less or no effect. Reactivity of the skin usually returns after six to twentyfour hours.
8. Local tolerance follows frequent exposure of a given area of skin. This result is transitory and rarely lasts more than a few days.
9. Relative transitory general tolerance follows frequent of large areas of skin.
10. Symptoms of general or constitutional reaction such as collapse and eosinophilia, follow reaction of large areas of skin in the case of extreme sensitiveness to light and

cold. Eosinophilia follows widespread reaction even in the scratch cases.

11. Adrenalin in dosage sufficient to cause a tremor does not prevent or relieve the reaction completely.

12. Passive transfer of hypersensitiveness to normal individuals without an inherited predisposition to allergic manifestations is probably impossible.

13. The symptoms are confined almost entirely to the point of contact, unless the reaction is severe. The ocular, nasal, and bronchial symptoms are not unlike those produced by pollen sensitiveness. In light sensitive cases, photophobia is very evident. Even temporary blindness may follow marked exposure to light. The abdominal symptoms amount to epigastric pain and dyspeptic symptoms which follow the ingestion of cold drinks or cold foods in some cold sensitive cases. This shows that the contact reaction can involve not only the skin, but also the mucous membrane, giving rise to marked local reactions.

The "reflex-like reaction" is a term used to designate reaction caused in tissues not directly exposed to the action of the physical agent. Reactions of this type may be confined to one locality or to one structure, such as the skin, nasal mucous membrane, bronchial tree, or may be widespread, involving several or many different structures. In Duke's series of 27 patients (12), the following reactions were observed and studied: orbital and nasal reactions caused by heat and cold, nasal reaction by the effect of light upon the retina, bronchial reactions

caused by heat and cold, skin reactions (erythema, pruritis, superficial urticaria) caused by heat and cold, deep urticaria and angioneurotic edema caused by heat and cold, severe abdominal pain caused by the ingestion of cold drinks or cold foods, diarrhea caused by the ingestion of hot drinks or cold foods, eosinophilia caused by heat and cold, and shock caused by heat. Twentyfive of the twentyseven cases were sensitive to heat or cold or to the combined action of both.

When these reflex-like reactions occur promptly their interpretation is relatively simple. When they are delayed, however, the interpretation is extremely difficult. They have the general characteristics which follow:

1. A family history of hay fever, asthma, or hives can be obtained in about fifty per cent of cases.
2. The reaction is characterized by erythema, edema, itching and activity of nonstriated muscle and secretory structures as caused by stimulation of the autonomic nervous system.
3. Sensitiveness may appear at any age but usually late in life.
4. The condition varies greatly in intensity from time to time. It differs markedly in this respect from contact reactions and from pollen reactions which are remarkably constant.
5. The condition does not seem necessarily to be permanent.
6. The skin is not exhausted locally by reaction so readily as with the contact reactions. Local tolerance does not necessarily follow frequent exposure to the irritating agent except as influenced by change in body temperature.
7. General tolerance frequently follows repeated exposure to

the irritating agent.

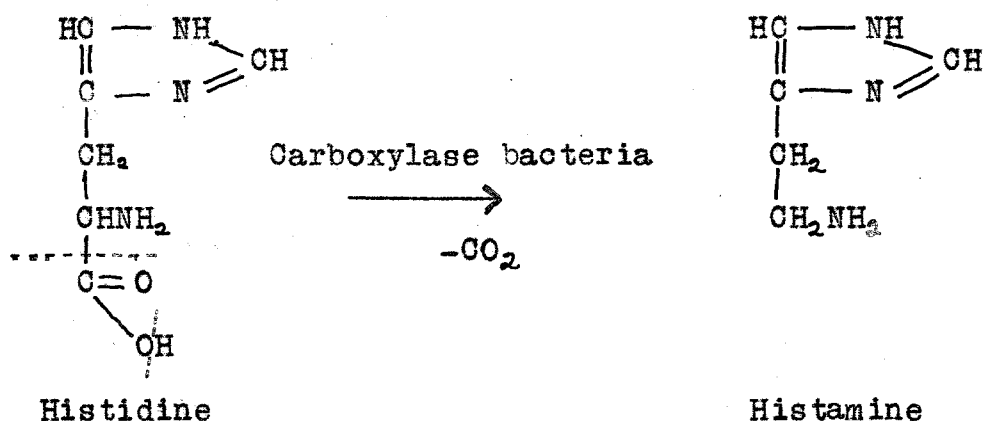
8. Symptoms of general or constitutional reactions, such as collapse and eosinophilia, may follow severe exposures in highly sensitive cases.
9. Adrenalin in small doses frequently relieves the reaction in cases that react promptly.
10. The reflex-like reactions are prone to be seasonal and apt to occur at certain times of the day or night and also at irregular intervals upon suitable exposures to the agent responsible for reaction.

## ETIOLOGY

The one explanation of the contact reactions which, in 1926, seemed to Duke (12) to be the most logical, is based on the assumption that patients with allergic tendencies might become specifically hypersensitive to some new body formed in the tissues solely under the influence of one specific physical agent, such as certain rays of light, heat or cold of certain specific grades, or possibly other analogous physical agencies. Since patients can become sensitive to and be made ill by the minute quantity of certain specific pollens, they surely could become sensitive to and be made ill by some unusual substance formed in the tissues under the influence of a physical agent.

It was shown by Barger and Dale (3) in 1910, that a protein split product, histamine, if injected subcutaneously into animals, produces bronchial constriction very similar to that found in animals dying in anaphylactic shock, and by Eustis (16) that if applied to the skin of human beings in a 1 to 1,000 solution, gives rise to a local hive reaction.

Since we shall find the substance histamine rather important in this discussion, I believe that an explanation of it's chemical and physiological nature will be of interest. Putrefactive bacteria in the intestine, acting on histidine, yield histamine. Histamine has been found in the contents of isolated loops of both the large and small intestine, and in the feces. (5) It is formed from histidine in the following manner:



Like other such products, histamine is filtered through the intestinal wall, picked up by the portal circulation and passed through the liver before it is thrown into the general circulation. When histamine is administered by mouth it disappears from the alimentary tract and exerts no demonstrable pharmacological effect. (5) In histamine shock, the blood volume is reduced owing to the passage of fluid through the walls of the capillaries, which the histamine renders more permeable. Subcutaneous injection of considerable doses of histamine produces vasodilation and lowers the coagulability of the blood. It accelerates the hemolytic action of the bile. After the injection of considerable doses of histamine fully half the plasma of the blood escapes into the tissues producing a great fall of blood pressure, and great increase of viscosity. (23)

We are primarily interested in the histamine in relation to the skin and it's action related to the cause of urticaria. This relationship will be brought out as well as possible in the following discussions. Other actions of histamine will also be noted.

The phenomenon of urticaria depends on the development of extra-cellular edema. Edema depends on the capillary permeability. Until twenty years ago the capillaries were thought of as simple endothelial tubes whose action was controlled by the condition of the arteries on the one side and the veins on the other. Observation has shown that the capillaries are covered by contractile cells (Rouget cells). These cells are probably concerned in the regulation of the size of the capillaries. The capillary tone can be varied without the intervention of the nervous system and seems to be determined by local conditions within and without the capillary endothelium. (26) Another discovery has been that a group of substances act as capillary poisons, causing increased permeability and dilatation. "These observations enable one to visualize the mechanism of the production of edema, and to explain the fall of blood pressure which accompanies traumatic shock and urticaria, through the tremendous increase in the number of open capillaries and their degree of dilatation and permeability." Rulison (26) further shows that dilatation alone is insufficient to cause transudation of plasma and since edema follows the use of histamine it is evident that a poisoning of the endothelial cells accompanies the action on the Rouget cells of the capillaries. In chronic ergotism this poisoning of the capillaries is permanent, resulting in gangrene. It is well known that histamine is the active constituent of ergot.

Grant (17) states that the urticarial reaction following, for example, a single firm stroke on the skin of certain susceptible subjects, known as "Urticaria factitia (dermographica), is brought



about by a complex mechanism set in motion by a diffusible substance probably akin in nature to histamine, which is released in the skin by the stroke. He further attempts to show that the evidence for the release of a histamine-like substance in urticaria factitia consists mainly in showing three things, namely (a) the close resemblance of the lesion in urticaria factitia to that caused by the introduction of histamine into the skin, (b) that the mechanism of the two reactions is the same, and (c) that certain phenomena of the histamine reaction which can only be interpreted as due to the presence of a diffusible substance in the skin are exactly reproduced in urticaria factitia. Grant made a series of observations with histamine on patients susceptible to urticaria factitia. The procedures are presented in considerable detail. His comparisons of the stroke and histamine reactions (the wheal) provide evidence strongly suggesting that a common cause is at work in the two cases. To compare the two reactions a firm stroke is made on the skin of a susceptible subject and near it the skin is pricked with a needle through a drop of 1 to 3,000 histamine placed on the skin. The urticarial reactions in the two places are very similar. The skin temperature during the course of the two reactions, observed by a thermoelectric couple, begins to rise soon after the appearance of the flush and subsides gradually with the reaction. If the venous pressure of the arm is raised 50 mm of mercury by constricting the veins, the rate at which both wheals develop is retarded, and under higher pressure (70 to 90 mm Hg) the wheals are fully reduced in size. If the circulation is occluded entirely, neither

stroke nor histamine wheal will appear on the skin. Both reactions are similarly affected by heating and cooling the skin (note- in these particular patients subject only to urticaria factitia or dermographism). Grant further shows that the reaction occurs equally well in the anesthetic as in the normal skin. This would lead one to believe that the reaction is independent of the nervous system. The flushes surrounding the wheal are due to a widespread dilatation of the arterioles. These are controlled by the nervous system, probably a secondary reaction, by a local nervous reflex. They are present when the nerves to the skin are freshly divided, but are wanting when the cut nerves have degenerated. In these experiments sufficient evidence is presented to show that the arteriolar flush with the histamine punctures is due to the presence of histamine and not due to the mechanical or painful stimulus of the needle prick. Grant further notes that the histamine and stroke stimuli are not only interchangeable, but also develop refractoriness upon repeated stimulation. He finds also that the same train of events takes place in the skin of normal subjects provided the injury is much more severe. Grant draws the conclusion from his work that "the urticarial lesion may be regarded as the expression of a general mechanism of defense in the skin against injuries of all kinds. It is the result of a purely physiological process and attracts attention in susceptible subjects because of the relatively mild grade of injury required to liberate the substance concerned."

Chen (8) made a series of observations on the course of experimental wheals repeatedly produced on the same areas of skin.

He speaks of sensitization and desensitization as the increase or diminution of the reaction without any reference to the special relations of the question of allergy. His experiments were made on human skin, as well as on that of dogs, and the results compared. The experiments on dogs did not show any significant differences. All injections were made intradermally. The urticariogenic substances used were morphine, histamine, atropine, and pilocarpine, each made into certain dilutions. In these experiments a local desensitizing effect following wheals produced by these chemical substances was regularly observed. The temporary cessation of wheal formation seems, according to Chen, to be a phenomenon independent of the nature of the urticariogenic substance, because the different substances produce also a desensitizing or refractory effect against one another.

Walzer (27) made a study of urticaria factitia (dermographism) upon forty-eight subjects, taken at random from the general run of cases in a dermatologic clinic, and thirteen subjects with urticaria and pruritis. He came to the conclusions that dermographism is a pathological condition, not an exaggerated normal one (as concluded by Grant). The demonstration of a floating principle in the blood as a cause of generalized urticaria factitia with the serum of ten patients with marked dermatographic symptoms, failed in all but one case, in which case a definite diagnosis as to the true condition of the patient could not be made, but it was probably a rather severe chronic urticaria with lichenoid dermatitis. The results of Walzer agree with those of Duke, in that physical allergy of the contact type cannot be

transferred readily to another person, with the technic used. It is conceivable, however, that the average patient may not contain enough dermographic substance; it may be in too high a dilution to manifest itself by such procedures.

Lewis (22) and his associates place the factitious wheal in the same category with the wheals of all types of urticaria, irrespective of the etiology. Lewis considers them defensive reactions of the skin to certain types of injury, and states that they occur in all persons, but in different degrees. He believes that all wheals are fundamentally the result of a common chemical causative factor - "a liberated substance or substances having a histamine-like action." These histamine-like substances, normal tissue metabolites, or "H-substance," as Lewis calls them, are liberated immediately either in considerable concentration or in excess in the skin, as a result of various forms of either internal or external trauma, and call forth the local vascular reaction which terminates the wheal. Lewis presents arguments to show that his H-substance simulates histamine more closely than it does any other substance employed for production of wheals, because not only do they both produce wheals, but, constitutionally, the reactions of these two substances are also similar. As part of the evidence to support this hypothesis, Lewis cited experiments in which many areas of the skin on the trunks of patients with urticaria factitia were stroked and whealed. This resulted in certain constitutional symptoms in the subjects, such as a general rise of cutaneous temperature, flushing of the face and a slight fall of blood

pressure.

Lewis believes that the traumatizing of many sites at the same time generates considerable amounts of this H-substance at the whealed areas, and therefore attributes the constitutional symptoms to traces of this substance which escape from the stroked areas into the general circulation. As the symptoms correspond closely to those resulting from the subcutaneous injection of minute doses of histamine, he concluded that the actions of histamine and this H-substance are identical in their constitutional results as well as in their local action.

Harris (19), working in Lewis' laboratory, arrived at the same conclusion as Lewis, and supports him in his views. By employing alcoholic extracts of human skin, he showed experimentally by physiologic evidence the presence of a substance in the normal skin extract which produced a wheal on intra-dermal injection. This substance is also a vaso-dilator and depressor. Harris was not able to isolate or definitely identify his substance chemically in the skin extracts, but, because of its similarity in the physiologic action, he expressed the belief that this extracted skin constituent is histamine or a histamine-like substance. He further showed that not only is it present in the cells of the normal skin in an easily disassociable form, but it is also easily released under such conditions as trauma.

Walzer (27) definitely states that he does not know what the dermatographism-inducing principle is. One thing however is certain; it is not histamine or the H-substance as suggested by Lewis in his writings. Such is this man's belief. "The fact that

all wheals may look alike clinically does not necessarily imply that the mechanism of all wheals are similar - that they are all fundamentally due to histamine." This is a bold statement by Walzer, and it seems to the writer, perhaps without foundation, even though he may be correct in his view.

It might be appropriate to state here that before it can be proven that histamine or some histamine-like substance is the underlying agent in urticaria, it will probably be necessary to have available a simple and delicate quantitative test for the substance.

I take the following study from Dale's series of lectures at the John Hopkins Hospital (10), in an effort to present a logical conclusion to some of the preceeding material. Dale gives a brief but complete review of the progress in the knowledge of histamine and it's related substances. He discusses the work of Lewis and of Harris (see above) and notes the thoroughness and cautious attitude of these men. From Dale's concluding statements upon the subject of histamine in general, I take the following quotation: "When we look at this more recent evidence as a whole, it does not appear to weaken the case for histamine as a chemical stimulant concerned in normal vascular and other body reactions. On the contrary, it seems to strengthen it, while giving it precision and defining more clearly the limits of it's validity. As the lines of that part of a general picture which the actions of histamine cover were more firmly drawn, the blank spaces, waiting to be filled by a similarly detailed study of the actions of other substances, came more clearly into view." Dale "mentions"

that a significant part in the vascular reactions may be played by choline, a substance much longer known than histamine as a natural body constituent.

Now from the immunologic point of view (9), allergic skin conditions might be divided into three groups. First, the underlying mechanism is specific and is characterized by a direct antigen-antibody reaction, so-called atopy, as is found in many cases of eczema and urticaria. The second group is non-specific and is characterized by the absence of antibodies in the blood or skin and by a lesion which is not due to the presence of an interaction between antigen and antibody, but due to an inherent sensitiveness of the skin to various forms of mechanical irritation as is seen in some cases of urticaria and dermatitis due to physical and chemical agents, as well as to other substances. Belonging in the third group are those in which there is both a specific and a non-specific factor involved. Dale, in his discussion (10), definitely states that the only factor from this viewpoint that is of value is the second, concerning the inherent sensitiveness of the skin.

It has been noted in previous discussions that some authorities believe all the allergic conditions may at sometime be explained upon the same basis. Some definite evidence toward this point of view has been supplied by Barber and Oriel (1) in their study of the blood in allergic conditions. They find from their experimental work and study that a more or less definite cycle of events takes place in all the acute allergic states so far investigated by them, for example, an attack of asthma, urticaria,

angioneurotic edema, or migraine, and the paroxysms of itching that occur periodically with prurigo and infantile eczema. In the period just before the paroxysm the following findings are reported. In the blood, the amino-acid content rises; the uric acid and creatinine are also apparently increased; and the chloride content of the whole blood (chiefly of the corpuscles) falls. In the urine, the free acidity rises; urates are often deposited when the urine cools; there is diminished water excretion, so that the specific gravity is usually high; there is retention of chlorides; the ether reaction is strongly positive; ammonia excretion rises and the ration of free acid to ammonia is altered, and the excretion of amino-acid, creatinine, and uric acid begins to rise. In the period following the subsidence of the paroxysm all those changes noted progress back toward their normal values.

Black (7) in a study of the blood sugar in allergic persons has found that the blood sugar and blood phosphorus run low figures in a considerable proportion of allergic persons. Black believes the possible etiologic significance of these findings is worthy of consideration as is their possible relationship to adrenal deficiency.

I find no references to work of this kind confined to the physical allergies alone. However, in consideration of the work of Dale, Barber and Oriel, and Black, one can readily conclude that the knowledge of all the allergies is still in it's infancy.

The reader will note that little has been said so far concerning the reflex-like reactions. Duke is the only man, I find, to have so far discussed this phase of the subject in the literature



in any detail. Duke believes that some of the reflex-like reactions, heat, effort and cold sensitiveness, seem to be due to a defect in the heat regulating mechanism of the body and caused very commonly by a febrile disease. He states that it can be caused apparently, also as a result of trauma to organs which play an important part in the regulation of body temperature. (14) He has found it occurring after skull fractures, brain hemorrhage, and in two cases after a stroke by lightning. Other occasional causes noted by Duke are cardiac or vascular diseases which impair normal circulation in one or several parts of the body. Also, disease in the endocrine organs, such as the adrenals or pituitary, which can alter normal vascular tone, or disease in the thyroid, which can alter metabolic rate; also disease in the intestinal tract, which can alter the absorption of histamine-like bodies, or disease which interferes with normal surface moisture, such as ichthyosis, or alters the normal caliber of the bronchioles, can sensitize to heat, effort, or cold. Duke notes that in younger people who are free from the host of organic diseases so frequently encountered in elderly people, he has been surprised to note how often the patient is physically normal and dates the illness from a febrile disease.

The evidence that Duke has found, causing him to believe the illnesses above described (reflex-like) are actually due to disorder in the heat regulating mechanism as follows:

1. The body temperature, especially in heat sensitive patients, is almost always subnormal, very frequently markedly abnormal and, in the more severe cases, extremely subnormal. Occas-

ionally, in heat sensitive cases, cases, body temperatures as low as 92 degrees F are observed. In addition, the temperature is unstable, and very often extremely unstable. It is often sent upward or downward by exposure of the skin to degrees of heat or cold which would have no effect whatever on the normal person, and could have little if any direct effect on blood temperature.

2. The basal metabolic rate is likewise inclined to be unstable and abnormal in this class of cases. This statement is based by Duke upon a quantity of data. Basal metabolism is often a little above normal or a little below normal and is often affected, to a marked degree, by the application of a little heat or cold to the skin or by effort. In one case of cold urticaria, a metabolic rate of minus 60 was repeatedly observed. (There was no evidence of myxedema in the case) When the metabolic rate returned to normal the patient was completely relieved.
3. A large proportion of heat sensitive cases are hyperesthetic to the effect of cold, in fact, the application of cold in degrees which would hardly be noticed by normal individuals may cause, in a heat sensitive person, a high grade of discomfort or actual pain. Conversely, cold sensitive cases are frequently hyperesthetic in high grade to the sense of heat.
4. The data upon which Duke's material is based was not obtained through history but instead through objective demonstration of the effect of heat, effort, and cold upon the afflicted

individuals.

Duke discusses the physiology of the heat regulating mechanism and it's relation to heat, effort and cold sensitiveness in a paper published previously to the above. (13) He has made a very thorough review of the literature upon the subject. A detailed study of this subject cannot be readily made in this paper without the presentation of an exhaustive amount of material. I will, however, attempt to summarize the subject.

The heat regulating mechanism is important and extremely complex and for effectiveness requires the coordinated action of many structures that control heat production and heat loss. Of structures that seem important may be mentioned sense organs and cerebral centers that have a thermostatic effect on heat control; several hormones that effect both heat production and heat loss; histamine-like bodies that effect vascular tone; three important cooling surfaces, namely, the mucous membrane of the nose, the bronchial membrane and the skin; structures that control the depth and rapidity of respiration and the rate of blood flow to surfaces and to active internal organs. For a comprehensive study of this phenomenon I refer the reader to Barbour (2), to Bazett (4) and to Duke (13).

Duke believes that under certain conditions this complicated mechanism is disordered at some point, and when disordered gives abnormal responses to sensations of heat and cold. Responses to heat and cold may then be inadequate to maintain ideal temperature, or exaggerated or in some cases perverted.

There are several points at which one could look for disease

which might affect the activity of the heat regulating mechanism and cause it to behave badly. These are: the sense organs and afferent nerve mechanism; the centers of the brain or cord which act as thermostatic regulators of temperature; the complicated nerve mechanisms controlling the caliber of vessels and modifying respiration and secretion of moisture and those that affect the metabolic rate. Further factors are the glands of internal secretion, debilitating diseases which weaken the organism and metabolic disturbances which disturb nutrition. Duke states that the part which might be played by histamine-like bodies in reactions of this type merits all the attention it may attract, as well as in the contact type of case.

## TREATMENT

It is only natural to suspect that many varied attempts have been made in the endeavor of physicians to treat cases of physical allergy, both when recognized as such and otherwise, and also that the greater majority of these attempts have been essentially unsuccessful. That is exactly what I have found in the literature, supplied by those few men who have had the courage or interest to report their cases. There is but one general method of treatment for all these illnesses which has been at all satisfactory in any large number of cases reported. This statement seems to be agreed upon by the various authorities. (27) Therefore I shall present this method as outlined by Duke in 1932. (15) The reader may note the poor results obtained in the three cases that are reported here. These are perhaps typical examples of many such cases the average physician may see.

Two types of physical allergy have been discussed, the contact type in which the reaction is confined to the area directly affected by the physical agent and the reflex-like type in which reaction occurs not only at the site of contact but in distant structures as well or in distant structures only. Both types may minutely resemble the allergies caused by material things, such as pollen or egg, and therefore have to be taken into account by physicians who treat hay fever, asthma and allied manifestations of allergy. Furthermore, in the treatment of physical allergy the same general principles of therapy can be used which prove effective in the treatment of other allergies, namely, avoidance of primary causes of illness, treatment of associated

illnesses, specific therapy with the causative agents, non-specific therapy and symptomatic treatment.

I will first discuss the treatment of contact allergy caused by light, cold or scratches.

Light Sensitiveness.— The treatment of patients who are highly sensitive to light demands adequate protection from exposure to light. Those persons who are highly sensitive can avoid exposure to light which is beyond their threshold by staying indoors on sunny days and by wearing black clothing or colored clothing (except blue) when out doors on cloudy days. They get along better in damp climates because of the fact that violet rays of light do not easily penetrate air moisture.

Tolerance for light can be developed through systematically increased exposures of increasingly large skin areas of the body to sunlight or to artificial light containing the rays which affect the patient. Daily exposures should be pushed to the point of causing slight reaction or stopped just short of this. The treatment may be started with exposure of about one-eighth of the entire skin area, and rapidly increased with the tolerance.

Patients who are sensitive to both light and heat should be treated with heat from a 15,000 watt nitrogen lamp rather than from the natural elements — this to be followed by treatment with ultraviolet light.

Symptoms of generalized shock which follow over-exposure of large areas of skin can be reduced by the use of adrenalin.

Duke states that it is possible in many cases to develop practical tolerance, that is a degree of tolerance which is useful to

the patient. If tolerance cannot be developed to such a degree, it may be necessary for him to change his habits, occupation, mode of dress and climate so as to afford himself adequate protection from light.

Cold Sensitiveness.-- Patients who are highly sensitive to cold must avoid exposure of large areas of skin to cold and must avoid situations and occupations which subject them to unavoidable exposure. Individuals of this sort can live comfortably in warm climates or in cold climates if they stay indoors when the outside temperature is low. Cold drinks and cold foods must be avoided.

Relative tolerance can be obtained in cold sensitive cases through application of cold water or ice rubs to gradually increasing areas of skin surface. Increased tolerance can be obtained usually within a period of two weeks.

Adrenalin subcutaneously relieves cases manifesting evidence of shock following accidental exposure of large areas of skin to cold.

Scratch Sensitiveness (Urticaria dermatographica).-- These cases may be made relatively tolerant by frequent brushings of the skin with a stiff brush. Improvement can almost always be expected. The symptom, itching, is almost completely relieved in a majority of cases within a few days, and the urticarial reaction and erythema are reduced in their intensity.

The reflex-like reactions, including the heat and effort sensitiveness, may offer the physician more difficulty both in diagnosis and in treatment.

Heat and Effort Sensitiveness (Urticaria Calorica).-- Sensitiveness to heat and to effort can occur separately, although as a rule if one is present the other can be demonstrated in slight or marked degree. Patients of this sort are tormented by the effect of heat and moist air and instinctively choose habits and occupation which do not subject them to over-heating beyond their tolerance. If such a patient is unfortunate, he is likely through over-heating to be prostrated or pitched into severe attacks of asthma, allergic coryza, urticaria, dermatitis, headache or shock whenever he is forced into situations in which he becomes heated beyond his threshold. These patients do much better in a dry climate whether warm or cold, "because of the easing effect of dry air upon the activity of the heat regulating mechanism."

Tolerance for heat can be raised in a great many cases if the patient's reaction to heat is not too severe. The average severe case requires the help of a nurse or some member of the family who can be taught to care for the patient and who can enforce treatment with heat, cold and effort. The tolerance can be raised for heat by applying the heat of a 1,500 watt nitrogen lamp to the skin from a distance of about 18 inches and continuing the application to the point of starting a reaction that is to the point of reproducing the symptom complained of by the patient. This should be immediately stopped or controlled by rapid rubbing of the skin with ice. Tolerance for heat can be raised appreciably in this way within a week or so in the majority of cases. In several of Duke's cases a few weeks treatment raised tolerance from a point where a five-second exposure to heat would cause re-



action to a point where a thirty minute exposure could be tolerated without apparent ill effect. This transforms an almost bedridden patient into an ambulant one.

After tolerance for heat has been increased in marked degree, tolerance for effort must be developed through subjecting the patient first to the effect of muscular effort and later to the effect of mental effort. A reaction precipitated by effort can be stopped as a rule by an ice rub. Tolerance for effort can often be increased by systematic exercise from the point where the effort of sitting up in bed precipitates reaction to where the patient can indulge in most of the activities required of him. It is needless to say that the patient will need confidence in his physician in order to follow out this treatment.

Heat and effort sensitiveness can be benefited or relieved frequently by treatment of other illnesses which contribute to the patient's discomfort. In a majority of cases, however, especially those which occur in younger individuals, no associated illness may be found.

Prolonged depression and inactivity or exposure to cold may intensify the reactions to heat and effort. However, a febrile disease usually gives temporary relief. Artificial fever therapy has been useful in some cases. Hot baths at midnight for the prevention of a drop in temperature from relatively normal to high grade subnormality may be effective in preventing early morning attacks.

Cold Sensitiveness.-- The cold sensitive case is more fortunate than the heat sensitive one because of the fact that effort in-

stead of causing illness usually gives relief. Patients can frequently gain tolerance for cold through the use of frequent cold baths. Frequently patients tolerate a rapid rub with ice better than a cold bath. Ice should be applied over the entire body and the rub should be stopped short of producing shivering.

## CASE REPORTS

### Case I: Urticaria Dermographica.

A white girl, aged 13, came to the University Dispensary, December 29, 1930, complaining of hives of a duration of two years which invariable occurred following any scratching or rubbing of the skin. The condition had been progressively worse during the past year. The past history is otherwise negative or unimportant.

The physical examination was essentially negative, except for the marked dermatographica. Blood examination showed a normal count with 5 per cent eosinophiles. Gastric and stool analyses revealed normal findings. No skin tests with the common foods or pollens were made.

A study of the family history reveals the following factors. There were nine children in the family. The father was living and well. The mother had had mild attacks of eczema. One brother and one sister were sensitive to pork. Another brother had hay fever every summer. One sister and one brother had symptoms similar to those of the patient. There were, in all, six and possibly seven cases of allergic manifestations in this family of eleven.

Tests with physical agents.-- A light scratch on the arm or back was immediately followed by a line of redness on the skin and itching, and within a brief interval by a line of edema, which persisted for about 20 minutes, then gradually disappeared. The patient was also affected by cold. If her hands were placed in cold water, they would react almost immediately, resulting in a large wheal covering the entire area of contact, the skin first becoming red and then white. Her face reacted in a similar manner

to cold.

Treatment given.- An autogenous vaccine was made from *Bacillus Coli* in the stool. A skin test with this vaccine gave a marked reaction. A series of subcutaneous injections were given, along with Sorium capsules. After six months of this therapy there was no improvement. The patient then failed to return for further treatment.

On March 11, 1935, the writer contacted this patient and her sister (see below). She has noted a small amount of improvement of the dermographica to the extent that it bothers her only with scratching or severe rubbing of the skin. Her hands and face have ceased to react to cold. She has taken no treatment since leaving the Dispensary.

Case II: Urticaria Dermographica.

M. A., aged 15 years, a sister to the girl in case I, entered the University Dispensary December 29, 1930. She presented the same symptoms as her sister, but in a more mild degree. The onset of the illness was about six months previous to her admission at the clinic. M. A. Differed from her sister in that she did not react to cold. The past history, physical and laboratory findings were essentially normal. The family history is noted above. The treatment given was a vaccine from the stool (like that of Case I) and the therapeutic results were nil.

M. A., like her sister, has taken no further treatment. Her dermographica has remained about the same over the period of five years.

Case III: Urticaria Calorica.

A white boy, aged 17, came to the University Dispensary, September 1, 1934, complaining of eruptions and welts on his skin following exercise such as playing tennis, chopping wood, or fast walking. This condition had been present for three years and was always worse in hot weather. It was accompanied by a severe itching and burning sensation. The eruption and itching would always gradually subside in three to four hours after the patient stopped the exercise. If he did not immediately rest, his face would swell so that he could hardly see. He would also become weak and somewhat dizzy with the more severe reactions.

The past history revealed nothing of interest. The patient did not have a febrile disease before the onset of his illness above.

The family history is of interest in that the father, aged 62, has hay fever. The mother, aged 57, has a chronic "bronchial cough." There are three other children in the family, none of which have shown any noticeable manifestations of allergy.

The physical examination showed a healthy, well nourished young man with no findings of note, except a mild dermatitis in the axillae and left crural regions, and a very mild dermatographica. Pulse 96, B.P. 111/70, weight 160 pounds.

The urine was normal. Blood count was not made. The basal metabolic rate was minus 10 and minus 4 per cent. (Benedict standard for men) The glucose tolerance test showed normal values. A series of skin tests showed the patient to be mildly skin sensitive (plus 1 reaction) to cat hair, milk, spinach, beet, blackberry, black raspberry and apricot. The patient was unable to recall

ever having noticed a reaction to any of these substances. An excessive erythema to local heat directly applied was noted, with no whealing. There was no reaction to the scratch test. The patient was not asked to demonstrate the reaction to exercise.

Treatment given.- The patient was directed to take frequent hot baths at increasing temperatures every day. In consideration of the basal metabolic rate, and of other cases of a similar nature reported in the literature (29) treated successfully with thyroid extract, thyroideum, grains 1 per day was administered, under careful supervision. After one month of trial, no results were obtained. The thyroideum was then discontinued and the therapeutic regime as described under urticaria calorica was started. The results of this therapy have not as yet been determined. A letter was sent to the patient who lives about 60 miles from Omaha, but no reply was received.

Comment.- If the reader is interested in studying case histories of all the various types of physical allergy, he will be benefited by referring to Duke's book (12) where typical cases are admirably presented and discussed at length. The cases presented above were those found available at the University Dispensary. The writer was fortunate in having attended one of these (case III) and in having been able to locate and talk to the other two patients.

### SUMMARY AND CONCLUSIONS

In this paper I have presented what I consider to be the important available contributions to the study of the cause of those illnesses included under the term "Physical Allergy."

I make no attempt to draw any conclusions, for, in the present state of knowledge concerning the physical allergies, no definite conclusion can be made as to their real cause. The evidence toward the relationship of the histamine-like substance is abundant.

The methods of therapy for the physical allergies which have proven to be generally successful have been discussed.

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